Symptoms and concerns among children and young people with life-limiting and life-threatening conditions: A systematic review highlighting meaningful health outcomes

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Abstract

Background**:** The design and provision of quality paediatric palliative care should prioritize issues that matter to children and their families, for optimal outcomes.

Aim**:** This review aims to identify symptoms concerns and outcomes, that matter to children and young people ("young people") with terminal illnesses and their families; it also aims to encourage the development of a relevant framework of health outcomes.

Study Design: This is a systematic literature review across multiple databases for identification of eligible primary evidence.

Data sources: Data sources such as PsychINFO, Medline, EMBASE, CINAHL, OpenGrey, and Science Direct Journals have been searched from 1 August 2016 to 30th July 2017. The study also incorporates consultations with experts in the field, citation searchers via Scopus, and a hand search for reference lists of included studies.

Results: Out of the 13,567 articles that have been evaluated, 81 studies were included. Of these, (n=68) are from high-income countries and (n=58) are cancer patients studies. A total of 3,236 young people, 2,103 family carers, 108 families, and 901 healthcare providers are included in the studies. Young people have not contributed to data in 30% of studies. Themes on priority concerns are presented by domain and health outcome; for example, 1) Physical (n=62 studies); e.g. physical symptoms, 2) psychological (n=65); e.g. worry 3) psycho-social (n=31); e.g. relationships, 4) existential (n=37); e.g. existential loss, and 5) "other" (n=39); e.g. information access.

Conclusion: Burdensome symptoms and concerns affect young people with malignant and non-malignant conditions and occur across the disease trajectory, so paediatric palliative care should not be limited to the end of life phase. A child-family centred framework of health outcomes, spanning the patient, family, and quality of service levels is proposed to inform service development. Future

research should address gaps identified; the involvement of the young people in research, evidence for developing countries, and for non-malignant conditions.

Keywords: person-centred outcomes; paediatrics; palliative care; young people; terminal illness

Key findings and implications of this manuscript

- An overarching theme identified in young people with malignant and non-malignant illnesses is the issue of multi-dimensional, complex symptoms and concerns which interact and occur across the disease trajectory.

- Our findings demonstrate considerable overlap in themes of illness experiences across diagnostic groups, settings of care and geographical location, alongside identifying common behaviours.
- This review presents an evidence-based child/family framework of symptoms, concerns and health outcomes. These span three levels; child, family, quality of services. This framework can encourage the development of paediatric palliative care outcome measures, to inform service audits, research, and evaluations.
- There is evidence that young people aged 6+ can self-report on symptoms, concerns and health outcomes, but reduced communication and cognitive abilities also remain a challenge. Developing person-centred child appropriate information and communication tools, which are, more inclusive of patients with special needs, should thus be prioritised.

- We highlight limited involvement of young people in research, a disparity in evidence coverage for developing countries, and a lack of evidence for non- malignant conditions.

1 Background

The number of children and young people ("young people") (aged 0-23 years) living with Life-limiting and Life-threatening Conditions (LLC) is increasing worldwide.[1-3] Of the 20.4 million people, annually who need palliative care towards the end of their life, approximately 6% are children. These data exclude factors such as the needs before the end of life and, thus, is an underestimation of the true needs of this group. Recent estimates have set the worldwide number of young people that need palliative care at any point during their disease trajectory at 21 million, with 8 million requiring some form of specialist palliative care.[4] The need for paediatric palliative care has been increasing over time; for example, in the UK, the prevalence of LLC in children increased from 25 to 32 per 10,000 population between 2000–2010.[5] In America, it is estimated that each year, approximately, 500,000 children are diagnosed with LLC and nearly 53,000 die from trauma, congenital conditions, extreme prematurity, and other acquired illness.[6] In low- and middle income countries, the HIV epidemic continues to pose a public health concern, and burden symptoms persist despite the advent of antiretroviral therapy. According to the Joint United Nations Programme, between 2.9-3.5 million children are living with HIV infection, with sub-Saharan Africa shouldering 91% of the global burden.[7] The situation is further exacerbated due to the increasing incidence and prevalence of various types of cancer among young people, with over 80% of deaths occurring in resource-limited settings.[8] This high mortality in resource-limited settings is largely attributed to health system challenges, such as late diagnosis, which limits curative treatment options,[9] and the poor coverage of supportive care services.[10] Besides HIV and cancer, complex chronic, neonatal, and other non-communicable diseases contribute to mortality and morbidity among the children in resource-limited settings.[11]

The current delivery of palliative care provision for young people typically runs parallel to existing health care systems, without integration of the existing and speciality services.[4] The provision of quality care to young people with LLC requires the critical establishment of robust evidence on the symptoms and concerns that matter to the patients and their families.[12] Despite the need for this

evidence, there is currently limited information on meaningful outcomes for young people with LLC.[12,13] This need for patient-level data is more pressing than ever amidst the worldwide demand to address the absence of person-centred outcome measures in the measurement of the quality of paediatric care.[13,14] Generating population-specific measures of Health-Related Quality of Life (HRQOL) is the key to developing palliative care for young people. Measurement of HRQOL will enable those developing and evaluating services to determine their effectiveness.[15] Furthermore, it can enable improvements in clinical care, research, and informed decision making.[16] Currently, there is no appropriate outcome assessment measure for use in paediatric palliative care.[15] In order to develop outcome assessment measures it is essential to understand the perspectives of the population in which they will be used.[17] At present, there is limited reporting on the needs and experiences of young people with LLC. In those cases where reviews of existing literature have been completed, they have been limited by inclusion of evidence from the North America alone[18] or focused solely on cancer and neuro-disability, neglecting other types of LLC.[18,19]

Research with young people with LLC is hampered by several methodological challenges. These include clinical considerations such as participants being very ill,[20] limited access to potential participants,[21] and limited capacity to generate self-reports due to the less developed (or impaired) verbal and cognitive skills of this population.[22] As symptoms and concerns affect children's beliefs, expectations, and perceptions, it becomes important for self-reports from young people to be prioritized wherever possible.[23] The inclusion of the perspectives of young people and their families is critical to ensure that outcome measures are meaningful to them and their families.[24] Regrettably, the level of young people's involvement in research remains limited and self-reports of their outcomes and experiences are not commonly reported.[25] Therefore, innovative and feasible approaches for engagement of young people in research that will shape their care should be prioritized.

This review aims to appraise the global evidence on symptoms and concerns that matter to young people and their families in order to identify meaningful core person-centred health outcomes in young people with LLC and their families. The objectives of this review are to: i) appraise the methodological quality and extent of research literature, detailing patient, caregiver, family, and health provider reports of symptoms and concerns across disease trajectories for young people living with LLC and their families; ii) identify the gaps that exist in the research literature (e.g. study design, countries, and conditions), and; iii) synthesise reports of symptoms and concerns, using a conceptual framework to identify the domains of importance in the development of outcome assessment measures for young people with LLC. These findings are utilised to discuss the implications for paediatric palliative care service development and outcome measurement.

2 Methods

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[26]

2.1 Search strategy

The databases searched were: MEDLINE via OVID (1946 –February week 4 2016), PsychINFO (1806 – February week 4 2016), EMBASE (1947 -2016 week 8 2016), CINAHL, Scopus (Elsevier) (1969 – 2016 week 8 2016), Science Direct Journals (Elsevier). Google Scholar and the OpenGrey website www.opengrey.eu/ [27] were used to identify relevant citations. Apart from the reference and citation searches, experts in the field were consulted to identify relevant literature. The search strategy was developed by the lead reviewer (EN) and a palliative care information scientist, after which it was reviewed by co-authors. The electronic search terms included combinations of Medical Subject Headings (MESH) and plain language words to capture the elements of the population (any life-limiting or life-threatening condition), intervention (palliative/ chronic, end of life etc.), and the

phenomenon of interest (symptoms, concerns, outcomes etc.). The detailed search strategy is presented in *Table 1*. The search was undertaken between January and August, 2016, and was updated on 31st July, 2017. Inclusion and exclusion criteria are presented in Table 1.

[Insert Table 1 here]

2.2 Compliance with Ethical Standards

This study is funded through an unrestricted grant provided by the Open Society Foundations. There were no additional ethical concerns, and all authors have no conflicts of interest to declare.

2.3 Data collection

The lead reviewer (EN) screened the titles and abstracts of all articles that have been identified through the search for relevance and has exported all such relevant articles to Endnote reference software version 7. The full texts of the articles have been obtained in cases where the abstracts did not contain sufficient information for determining the relevance of an article. Any duplicate references were removed. Two independent reviewers (EN, MA) reviewed the titles and abstracts of the remaining references against the following criteria:

Inclusion criteria:

i. Focus on life-limiting and life-threatening conditions as defined by the WHO
ii. Focus on meaningful health outcomes in children and young people with life-limiting and life-threatening conditions and their families
iii. Mixed age groups studies that provide age-stratified results
iv. Case studies of at least three participants
v. Qualitative, quantitative, and mixed method studies

Exclusion criteria:

i. Case studies of just one or two patients

ii. No report on symptoms/concerns and preferences for children living with life-limiting and life-threatening conditions
iii. Focus on the needs of the family alone (i.e. excluding the child)
iv. No empirical data (editorials, reports, letters, reviews, discussion papers, commentaries and case histories)
v. Insufficient information to judge inclusion eligibility
vi. The full paper could not be obtained

Articles not meeting the inclusion criteria were discarded. Relevant studies were subsequently reviewed based on the following characteristics: (i) source of study, (ii) year of publication, (iii) study aims as reported, (iv) age range or mean age, (v) primary diagnosis as reported, (vi) study design, (vii) sampling approach, (viii) number and type of study participants, (ix) data collection methods, (x) setting, and (xi) key findings related to phenomenon of interest. Disagreements were resolved through consultation with senior researchers.

2.4 Assessment of methodological quality of studies

All studies have been assessed for methodological quality using the Hawker checklist for reviewing disparate data systematically.[28] Ten components[28] have been assessed for methodological rigour with a possible range of scores (good=4, fair =3, poor =2, and very poor =1). No studies have been eliminated based on quality criteria. The STROBE checklist has been referred to for enhancing the clarification of observational studies.[29] Two authors have independently assessed and rated the included studies for rigour and methodological quality. The independent scores by the two authors have been compared for consistency. Any inconsistencies have been resolved through consultation with experts (RH, FM, and KB). The inter-rater agreement was computed using the Intraclass Correlation Coefficients (ICC) and Cohen's Kappa statistic for the methodological and grading datasets. Decisions on acceptable levels of agreement were based on the following cut-offs: poor <0,

slight (0.0-0.2.), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), and almost perfect (0.81-1.00).

2.5 Analysis
2.6 Data extraction

Data from studies that met the inclusion criteria were extracted into Microsoft Excel spreadsheets, which has been piloted by the lead reviewer templates (see Table 2)., Quotes to support reported themes and original author notes have been extracted for qualitative studies. The identified outcome measures have also been extracted into a pre-designed Microsoft Excel template and assessed for quality of measurement properties using the COSMIN checklist.[30]

2.7 Data synthesis

The data has been synthesised using a systematic review and integrative design.[31,32] Both qualitative and quantitative narrative syntheses approaches have been used. Descriptive statistics have also been used to summarize the studies under selected subheadings such as country, setting, focus, diagnosis, characteristics of respondents, and the main themes identified. Descriptive themes, encompassing the themes or codes of the primary studies, have been developed with attention to similarities and differences across and between studies, and then grouped by phenomenon/themes. Disagreements have been resolved through discussions, guided by references to results, discussion, and conclusions sections of included studies and through consultation of content experts. Data has been assessed for contrasting themes within different diagnostic groups and by developmental age, grouped as follows: (0-5 years, 6-9, 10-14, 15+); it has been based on guidance on feasibility as informed by included studies, best practices[33,34] and expert guidance.

Subsequently, a conceptual framework of domains underlying the concept of health outcomes has been developed. A reference has been made to the WHO definition for paediatric palliative care and the core domains have been mapped out; physical, psychological, social, and spiritual/existential.[35] A fifth

domain, "other", was adopted to accommodate any themes and sub-themes that did not seem to fit into the existing four domains. References have been made to WHO definitions for health,[36] the Patient-Reported Outcomes Measurement Information Systems (PROMIS) framework,[37] and related literature,[18,19,38,39] in order to aid the labelling of themes and sub-themes, while seeking expert guidance (FM, KB, RH) where necessary. The lead reviewer has further coded the data by domain, themes, and sub-themes, documenting illustrative examples of the outcomes. Two content experts (RH, SE) have verified that the coding and areas of disagreement have been resolved through discussion and consultation of experts.

3 Results

3.1 Study selection process

A total of 13,569 articles were identified, after eliminating the duplicates. These were assessed for eligibility, after which 81 have been included in this review; of these 81, 79 were original studies, published between 1996 and 2017 (*see Figure 1*).

[Insert Figure 1 here]

3.2 Characteristics of included studies

Of the 81 included papers, 68 (84%) are from high income countries [USA (n=22), Canada (n=15), Sweden (n=9), UK (n=9), Australia (n=3), Japan (n=2), Netherlands (n=2), Germany (n=1), Hong Kong (n=1) , New Zealand (n=1), Spain (n=1), Switzerland (n=1), 1 multi-country [UK and Australia n=1], and 13 (16%) from low-middle income countries [Lebanon (n=1), Malaysia (n=1), Taiwan (n=1), Thailand (n=1), Jamaica (n=1), Brazil (n=1), South Africa (n=2), Uganda (n=1), Malawi (n=1), Nigeria (n=1), Zimbabwe (n=1), multi-national Uganda and South Africa (n=1)].

A total of 2,951 young people, 545 parents/family carers, and 401 professionals are represented by the included studies. Respondents, as reported by studies, are as follows; young people (n=29), parents (n=14), health workers (n=6), parents/young people and siblings (n=21), young people/parents/health workers (n=7), and clinical file reviews (n=4). Forty-five (55.6%) of the studies are qualitative, 27 (33.3%) are quantitative (of which four were clinical file reviews), and 9 (11.1%) are mixed methods. As presented in Table 2, a range of approaches for data collection and analysis have been adopted. The focus of the papers varies, including a focus on symptom experiences (n=42; 51.9%), outcomes (n=20; 24.3%), friendship dynamics (n=1; 1%), scale development (n=4; 4.9%). and end-of-life care experiences (n=14; 17.3%).

[Insert Table 2 here]

Most of the studies (n=58; 71.6%) involve cancer patients; of these, 46 studies provided details on types of cancer, with treatment status reported in all studies (Table 3).

[Insert Table 3 here]

3.3 Quality of included studies

The level of agreement on the quality of study appraisal scores is good (ICC=0.80.). Hawker's quality scores range from 20 to 38, out of a possible score of 40. The mean and range scores for qualitative studies was 31 (range 21-38), 29 for mixed method studies (range 21-36) and 31.2 for quantitative studies (range 20-38). These studies are mainly descriptive, non-experimental, and cross-sectional, with some of them using convenience samples; one randomized controlled trial is included[40] (see Table 2 for details). The quality of included studies is poor in the following domains: ethics, bias, sampling, and limited articulation of the generalisability of the findings. In most instances, the discussion of ethics has been limited to seeking approval from ethics review boards; assent and consent processes have rarely been explained in detail. It is found that only two papers have mentioned the use of child-appropriate information sheets.[41] Extremely few studies have mentioned the consideration of respondent age in questionnaire development as a way of ensuring age-appropriateness of the questions. [41-48] The process surrounding data collection with young people has rarely been explained in detail.

For 12 qualitative studies, the setting of the interviews and discussions has been provided, including quiet locales and open areas. [49-60] A majority of qualitative studies fail to account for potential bias from researchers. Only three qualitative studies validated the findings, using focus group interviews [52,55] or documentary analysis for triangulation.[41]

3.4 Aspects of the health of young people with life-limiting illness and their families

The full thematic of findings are presented in Appendix 1 and key findings are explained in the following section by domain.

[Insert supplementary results appendix 1 link here]

3.5 Physical (n=62 studies; 77%)

3.5.1 Physical symptoms and concerns

Disease and procedure-related pain has emerged as a major concern across the disease trajectory, and during the end of life stage; the pain is often reported as 'intolerable', or 'out of control', with procedure-related pain being associated with fear, anxiety, and suffering.[61,46,62-74] For this reason, the need for parental protection and assistance during treatment is stressed upon in cases of young children with cancer.[46,75] Two studies have found such pain to be more prevalent in children with solid tumours.[76,77] Inadequate treatment of pain, side effects of opioids, and treatment of non-pain related symptoms have also been mentioned as concerns by paediatric oncology patients.[61,69] Concept elicitation and illness experience studies highlight pain control as a priority in cancer and non-cancer disease groups.[19,27,58,60,78-81]

Other commonly reported physical symptoms are lack of energy, nausea, vomiting, dry mouth, weight loss, and drowsiness[63,71,82-84 27,65,71,82,83,85-88]. Symptoms associated with severe distress during cancer treatment include difficulty in swallowing and shortness of breath.[63,89] Symptoms associated with severe distress include shortness of breath, feeding difficulties, fatigue, drowsiness, nausea, loss of motor function, pain, reduced mobility, decreased appetite, respiratory failure, and lack of energy. [46,62,64,65,90,91] Difficulty in breathing/shortness of breath, fatigue, drowsiness, and nausea is a common concern at the end of life, in both cancer and non-cancer patients.[62,64,65,68,76,91,92,90] Providing support with eating, sleeping problems, and minimizing symptom distress are commonly expressed as the end of life care priorities.[60,93,94] In two studies**,** neurological deterioration, loss of the ability to communicate, and decreased physical activity have been associated with impending death.[56,95]

On-going seizures are a major concern among epilepsy patients.[96] Weight loss, fever, mouth sores, stunted growth, diarrhoea, wasting, lymphadenopathy, oral candida, acute malnutrition, pneumonia, and respiratory tract infections are common in paediatric patients with HIV.[87,97,98] One study conducted

among HIV positive children, aged 6-15 years, reported a high prevalence of other morbidities such as hearing impairment, visual impairment, gingivitis, speech impairment, and gross motor deficits.[98] The end-stage renal failure patients have also reported physical needs of post-renal transplant adjustment and coping;[99] their dependence on and need for a wheelchair compromises their function and has been associated with negative emotions.[99]

Studies that address concerns in neuro-disability and, particularly, the one on the development of the suffering scale in adolescents with cancer, prioritised physical symptoms and associated distress as core domains, which should be included in outcome measures for young people with LLC. [27,58] It is noticed that children tend to use unique language to describe their symptoms and, at times, have difficulty explaining their feelings.[100] [45,101] The 'no symptom' syndrome is also reported in one study and has been interpreted as a form of denial, lack of specific symptoms, or unchanged health status.[65]

Young people express the need to be normal with full ability to perform age-appropriate functions such as self-care, mobility, and physical activity.[82,83] [51,54,95,99,102-107] Symptoms become more of a concern when they lead to physical and mental changes or affect the ability of young people to engage in daily activities. [44,46,49,67,95,103,104,108,109]

3.6 Psychological (n=65 studies, 80%)

The psychological consequences of living with LLC span a spectrum of sub-domains including emotional, mood-related, cognitive, behavioural change, and isolation. Based on observations, children aged 0-6 years express a need for emotional satisfaction and expression of their own will.[75] Mood-related symptoms include emotional instability[27], feeling shy about living with the disease,[80] feeling horrible, furious, upset, and disappointed[99], angry, scared, bored, sad, nervous, and crying. [45,49,50,58,91,104] [80,86]

Children receiving cancer treatment commonly experience mood swings, depression, anxiety, and lack of concentration.[46,63,71 110] At the end of life, psychosocial symptoms of cancer patients include fear of going to sleep and dying, displaying a distance from family, confusion, anxiety and depression, irritability, inability to laugh or smile, insecurity, and mood swings. [42,46,65,76,82] One study has found emotional concerns to be more dominant in older age groups (12 and above).[83] Palliative care professionals mention the need for alleviation of psychological suffering as an important domain of quality of life in paediatric palliative care.[107]

Cognitive changes that have been identified include disturbance of consciousness, declining attention and concentration orientation, social skills, cognition, energy, and drive. [57,76,80,81,84] Other concerns include the need for a sense of self-worth,[111] resilience, coping with illness, accepting the present pain for potential gain in future, and the desire to protect other people from similar illness experiences. Children have sometimes reported psychological growth; for example, on achieving milestones like treatment completion, they reflect on the whole experience cognitively; "they either felt the same as old- not having noted any changes on outlook to life, completely different, or not normal."[112] School-going children have also reported poorer performance at school.[58 110]

Parents of young people report a common range of behaviours in their children: anti-social, disobedient, unwilling to take medication, creating difficulties in incorporating daily medication into their routine schedules, and pill burden associated distress.[73,96,99,102,103,113,114] Adolescents (aged 12-18 years) are concerned that isolation or being like a "prisoner" has radically altered their lives and made it alien to them; some have cited memories of fear that could not be forgotten.[46] Hospitalisation, for treatment, is associated with isolation, affecting opportunities for interaction with friends and siblings, and invoking emotions of sadness, and homesickness.[104,109] The impact of living with LLC on social

and physical functioning leads to feelings of frustration regarding a strong wish for 'normalcy'. [46,56,103,108]

3.7 Psychosocial (n=31 studies; 38%)

Young people and their families perceive living with LLC as a stressful life experience, irrespective of the type of diagnosis. Some concerns reveal a social and physical health overlap (e.g. young people with epilepsy who "felt different" due to their need for medication[96]). For paediatric HIV patients, disease-related features such as skin rash and facial lipodystrophy have been found to be associated with stigma.[115] Paediatric cancer patients are more concerned about hair loss and skin changes, which affect their body image.[95,116] The experiences of becoming the centre of attention to peers, being bullied at school, and isolation, have been prominently expressed. [52,72,96,102,114,116,117]. Young people who have received liver transplants cite the plight of post-treatment features such as large scars, clubbed fingers, and short stature.[72]

Hospitalisation is a particularly undesirable experience associated with disruption of school schedule and social interaction, and resulting in isolation.[23,44,49,50,54,58,72,82,99,106,108,116] Young people generally value social relations where they feel comfortable talking, being listened to, share secrets, and are treated with respect.[23,39,60,72,96,108 118 107] Young people, health professionals, and families express the need for children to experience fun, humour, laughter, recreation, and leisure alongside treatment.[23,27,51,60,95,108 107]

Family relation concerns have been highlighted in 20 studies.[19,39,41,44,46,52,58,72,73,75,96,103,109,115,119-125] Young people value support from their families as it is a structure that helps them feel comfortable and secure. Concerns regarding lack of family support have also been reported; children report discomfort in having to deal with expressions of anger, shock and sorrow from their parents/caregivers, which

engenders a sense of being a burden.[46,124,125] Young people are worried about their family carers/parents emotions of fear, hopelessness, depression, and anxiety.[52,72,95,96,115,119]

Older children have raised concerns regarding receipt of information about their diagnosis directly from the right people, rather than by overhearing parents and physicians. [103,109,114,126] Some young people prefer to keep their diagnosis a secret from peers for fear of social stigma. [96,103,109,114] In three studies, adolescents have reported concerns relating to sexuality. These concerns include initiating and maintaining romantic relationships, painful sex, and fertility concerns after treatment.[103,109 88]

3.7.1 Existential/spiritual/religious (n=37;46%)

The concerns under this category include existential loss, existential vacuum, worry about death, not being at peace, uncertainty arising from inability to anticipate situations, a need to be remembered, hopes, and finding meaning in life in situations, especially when young people feel that their dreams and hopes for the future are being ruined due to terminal illness. [39,54,58,67,78,79,95,108,110,117,127,128] In one study, health professionals have noted that the "life goes on" ideology is important.[107] It is common for the young people, including three-year-olds, to end their narratives with concerns about impending death.[129] Young people and families have also expressed the construct of connection to something larger than the self. These beliefs seem to help them build resilience.[47,92,95] The desire for religious prayers has been mentioned in several instances as a priority.[59,108] The young people have also reported a sense of spiritual growth in maturity and some are thankful for the "gift of life" and wish to protect others from similar experiences.[93,130]

3.8 Other concerns (n=39; 48%)

Besides physical, psychological, psychosocial, and spiritual/existential concerns, additional pressing problems have also been found; they include communication and information, decision making, and care provision concerns (see *Table 4* for details).

[Insert Table 4]

3.9 Sub-group analysis by age group and type of diagnosis

The differences in symptoms and concerns that matter to young people, with respect to age and type of diagnosis, are noted in this study; the results for the same are presented in Table 5. For example, treatment procedural pain and alienation are more dominant in younger children (0-5 years), while an existential loss, self-image, and need for access to information are more dominant in older children (6-9, 10-14, 15+) years.[131]

[Insert Table 5]

Symptoms and concerns that have been identified for young people with LLC and their families are mapped in a summary diagram, alongside illustrative examples of useful health outcomes, in *Figure 2*.

[Insert Figure 2 here]

4 Discussion

Through the process of drawing together a comprehensive body of literature across global regions and different conditions, this paper identifies the symptoms and other concerns faced by young people with LLC and their families. Previous reviews have focused solely on cancer and neuro-disability.[18,19,132] This synthesis and presentation of symptoms and concerns across core health domains can be used to guide the development of outcome assessment measures for paediatric palliative care. While the studies are of intermediate methodological quality, it has been possible to extract data on what young people with LLC consider as important, to inform the development of the child/family centred conceptual framework. Studies in this review recruited patients at different stages of the disease trajectory, but multi-dimensional burdensome symptoms and concerns were found across studies. This finding informs debate around the appropriate timing of referral to, and the initiation of, paediatric palliative care (i.e. soon after diagnosis vs. later in the disease trajectory and towards the end of life). The key message is that, for optimal outcomes, paediatric palliative care should be provided from the time of diagnosis and through to death and bereavement, as is recommended by the World Health Assembly.[35] This approach would align with recent evidence demonstrating the benefits of providing early integrated palliative care in adult populations.[133]

The themes concerning symptoms and concerns that have been identified in this review are embodied in illness experience and multidimensionality and are underpinned by the three overlapping domains of child, carer/family, and quality of services. This is in agreement with proposed models of care in palliative care, recommending the incorporation of these components in outcome assessment.[134] Given the task at hand - that of meeting such multi-dimensional concerns - paediatric palliative care models of care may benefit from key elements that have been proposed for person-centred care, which include respect, coordination and integration, physical comfort and emotional support, involvement and support for carers/family, information and education, continuity, and transition.[135] Person-centred care also proposes key activities such as personalised care, self-management support, and shared decision making.[136] This ethos embraces the core child/family concerns that have been identified in this review. The review findings also demonstrate the intrinsic link between child and carer/family, and care provider interactions, as reflected under the quality of services domain. Positive engagement through information, education, and communication has the potential to enhance child/carer/family self-efficacy and self-management, which can have an impact on outcomes of care. Positive provider interactions may explain the manner in which system process related concerns link to the optimal goals of care and the reasons for their importance. An important consideration for development of services for young people with LLC is the development indicators that can be used to assess the structure, process, and outcomes aspects of health services. This review makes an important contribution by putting forward an evidence-based child/family framework of domains, from which such indicators could be selected. This makes it easier for care providers to gather more information about the relevant domains some of the constructs and symptoms to facilitate prompt action.

The information and communication theme identified in this review warrants further exploration in young people with LLC. Young people are a unique population with varying symptoms and concerns which occur alongside continuing physical, emotional and cognitive development, and a dynamic

socio-ecological environment.[33] Indeed, several studies have highlighted the uniqueness of the language that children use to describe their symptoms and concerns.[18,101] Furthermore, paediatric palliative care patients may also have reduced communication and cognitive abilities.[15] This review highlights the ability of young people (6+ years) to self-report on symptoms and health outcomes. As such, young people should be central to and involved in the elicitation of preferences and development of outcome measures. Such an approach should be aligned with simultaneous investment in appropriate information and communication tools and strategies. It is time to prioritise the provision of self/proxy reporting options for outcome measures in paediatric palliative care to make self-report a preferred option for subjective outcomes, whenever possible.[34,137,138]

This review identifies differences in the way health concerns, such as social and psychological well-being, are expressed on the basis of developmental age. With age, the cognitive, emotional, and socio-ecological aspects of children undergo change. For example, an advanced understanding of illness emerges in adolescents[139] alongside a shift towards a preference for self-efficacy and shared decision-making models.[83] Although the core domains of health remain robust across adult and paediatric populations, the developmental age of young people needs to be considered. Differences across cognitive, emotional and socio-ecological facets render the use of adult-based measures inappropriate, even with adolescents.[137]

It is observed that young people have not been interviewed in 30% of the studies, and 35% are mixed samples of young people and proxies, suggesting a low level of involvement of young people in the research that aims to inform the direction of their care. The findings echo previous reports about children with cancer.[25] Involving young people in research that informs their care is the first step to allowing their experiences to update the models of care; this is far from commonplace across the literature. In order to guide best practices on research involving young people, methodological

concerns regarding the following need to be addressed: the use of age-appropriate methods of data collection; question wording; duration of interviews; processes of data collection; the manner in which challenging issues of interviewing ill children are dealt with; provision of sufficient details on recruitment strategies, and; informed consent processes .[12,33]

The review observes considerable overlap across themes related to the subjective experiences of illness across diagnostic groups, study locations, and age groups of children. For example, there are parallels in themes identified across previous reports in paediatric cancer, [18,132] paediatric HIV,[140] and paediatric neuro-disability.[19] Furthermore, similar indicators have been found that are useful for comparing models of care across different settings.[135] This enhances the feasibility of multi-setting comparisons.[141] It also lends credibility to the use of generic palliative care outcome measures in children with LLC, with minor adaptations wherever necessary, for aspects such as health status, the process of care, or socio-cultural concerns.[142] There are over 300 LLC conditions experienced by young people that may require palliative care; the development of disease-specific outcome measures across all conditions may not be appropriate or feasible, moreover users want fewer tools.[143] [144,145]Overlap in the conceptualisation of health outcomes in paediatric palliative care can support the growth of the research field.[137]

5 Strengths and limitations

To reduce bias, the review adopted a broad and comprehensive search strategy across multiple databases, did not limit article inclusion by language, and involved field experts to identify any additional relevant literature. The search has been conducted following PRISMA guidelines. The quality of studies was also assessed, although not used as a basis for article exclusion. This is the first review to comprehensively appraise the state of evidence on symptoms and concerns in young people

with a broad range of life-limiting and life-threatening conditions, across the disease trajectory. This is also the most comprehensive framework of meaningful outcomes for young people with LLC.

This review has some limitations. Data from a disparate evidence base has been compiled, which utilises a wide range of methods to understand the symptoms and concerns of young people. The variety of approaches meant that it was not possible to assess the extent or magnitude of identified symptoms and concerns among study participants. The inclusion of studies, with both qualitative and quantitative approaches, led the team to adopt narrative methods of synthesis, with efforts made to be transparent about how this was undertaken. Furthermore, some studies did not report the recruitment strategies and as such potential bias could not be assessed, compromising our judgement regarding the methodological quality of the studies included.[146] Many conditions require palliative care and different terminologies are used in different settings and consequently relevant articles may not have been identified.[143]

6 Implications for research and practice

There is a high burden of interacting and multidimensional symptoms and concerns in paediatric palliative care populations. These occur across the disease trajectory, in both malignant and non-malignant conditions. Therefore, early integration of paediatric palliative care into care plans to address these issues is recommended.

A skilled multi-professional team will be needed to address the symptoms and concerns raised, given they are so wide-ranging. This study challenges the unidimensional or typical biomedical models of care for children with LLC, which fail to comprehensively address their multi-dimensional symptoms and concerns. This child/family centred framework of child/family domains, grounded in their illness, mirrors the structure, process, and outcomes domains of health service improvement, and can guide the development of appropriate outcome measures to assess existing services and support their development.[15] The measures will inform service audits, research, and evaluations in order to stimulate

service development. Developmental age will be important to consider when developing paediatric palliative care outcome measures, with differences across young people identified across the emotional, cognitive, and socio-ecological levels in this review. The developmental age categorizations that have been used to explore these variations in this review were broad and future studies should explore this further, using narrower categories or those that have been recommended for paediatric palliative care.[139] Our findings indicate commonality in the illness experience, suggesting that unified person-centred outcome measures for children across different diseases are feasible. It is instead developmental age which may determine variations in the domains (content) and form of a measure.[147]

Internationally, the state of science remains poor for aspects of care for young people with LLC, including spiritual/existential concerns, patient-reported experiences of care, service delivery, decision-making information, and approaches to communication.[132] Future studies should further explore these areas, alongside addressing gaps in evidence on symptoms and concerns for young people with LLC with non-malignant conditions, those in developing countries and those from different social-cultural settings.

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Contributors' Statements

Eve Namisango conceptualised and designed the study, reviewed literature, abstracted and analysed the data, and drafted the initial manuscript.

Professor Richard Harding, Professor Fliss Murtagh, and Dr Katherine Bristowe reviewed the protocol, data abstraction tools, data analysis framework, and the results.

Professor Irene Higginson and Dr Melanie Abas reviewed the research questions, search strategy, and review findings.

Dr Matthew Allsop reviewed the protocol, abstracted data, and carried out data analysis in association with the lead reviewer.

Professor Julia Downing reviewed the analysis framework and appraised the interpretation of the review findings.

All authors have contributed to the final manuscript.

7 References

1. Fraser LK, Miller M, Hain R, et al. Rising national prevalence of life-limiting conditions in children in England. *Pediatrics* 2012; **129**(4): e923-9.
2. Burns KH, Casey PH, Lyle RE, Bird TM, Fussell JJ, Robbins JM. Increasing prevalence of medically complex children in US hospitals. *Pediatrics* 2010; **126**(4): 638-46.
3. Downing J, Birtar D, Chambers L, Gelb B, Drake R, Kiman R. Children's palliative care: a global concern. *International Journal of Palliative Nursing* 2012; **18**(3): 109-14.
4. Connor SR, Downing J, Marston J. Estimating the Global Need for Palliative Care for Children: A Cross-sectional Analysis. *J Pain Symptom Manage* 2017; **53**(2): 171-7.
5. Fraser LK, Miller M, Hain R, et al. Rising national prevalence of life-limiting conditions in children in England. *Pediatrics* 2012; **129**(4): 2011-846.
6. Pfund R, Fowler-Kerry S. Perspectives on Palliative Care for Children and Young People : A Global Discourse: Oxford UK Radcliffe Publishing Ltd,; 2010.
7. Organisation WH. PROGRESS REPORT 2016 PREVENT HIV, TEST AND TREAT ALL. Geneva Switzerland World Health Organisation 2016.
8. World Bank. Country and Lending Groups. 2012.
9. International Agency for Research on Cancer. World Cancer Report 2014
10. Israels T, Kambugu J, Kouya F, et al. Clinical trials to improve childhood cancer care and survival in sub-Saharan Africa. *Nat Rev Clin Oncol* 2013; **10**(10): 599-604.
11. Connor SJ, Sisimayi C, Garanganga E, Ikin B, Ali Z. Assessment of the Need for Palliative Care for Children Three Country Report: South Africa, Kenya and Zimbabwe, 2013.
12. Beecham E, Hudson BF, Oostendorp L, et al. A call for increased paediatric palliative care research: Identifying barriers. *Palliat Med* 2016; **30**(10): 979-80.
13. Johnston EE, Rosenberg AR, Kamal AH. Pediatric-Specific End-of-Life Care Quality Measures: An Unmet Need of a Vulnerable Population. *J Oncol Pract* 2017; **13**(10): e874-e80.
14. Mangione-Smith R. The Challenges of Addressing Pediatric Quality Measurement Gaps. *Pediatrics* 2017.
15. Coombes LH, Wiseman T, Lucas G, Sangha A, Murtagh FE. Health-related quality-of-life outcome measures in paediatric palliative care: A systematic review of psychometric properties and feasibility of use. *Palliat Med* 2016; **31**: 0269216316649155.
16. Hearn J, Higginson IJ. Outcome measures in palliative care for advanced cancer patients: a review. *Journal of public health medicine* 1997; **19**(2): 193-9.
17. de Wit M, Abma T, Koelewijn-van Loon M, Collins S, Kirwan J. Involving patient research partners has a significant impact on outcomes research: a responsive evaluation of the international OMERACT conferences. *BMJ Open* 2013; **3**(5).
18. Ruland CM, Hamilton GA, Schjodt-Osmo B. The Complexity of Symptoms and Problems Experienced in Children with Cancer: A Review of the Literature. *Journal of Pain and Symptom Management* 2009; **37**(3): 403-18.
19. Morris C, Janssens A, Shilling V, et al. Meaningful health outcomes for paediatric neurodisability: Stakeholder prioritisation and appropriateness of patient reported outcome measures. *Health and Quality of Life Outcomes* 2015; **13**.
20. Addington-Hall J. Research sensitivities to palliative care patients. *Eur J Cancer Care (Engl)* 2002; **11**(3): 220-4.
21. Steele R, Cadell S, Siden H, Andrews G, Smit Quosai T, Feichtinger L. Impact of research participation on parents of seriously ill children. *J Palliat Med* 2014; **17**(7): 788-96.
22. Clark A. Young children as protagonists and the role of participatory, visual methods in engaging multiple perspectives. *Am J Community Psychol* 2010; **46**(1-2): 115-23.
23. Evan E., Calonico E, Tan J, Zeltzer L. A Qualitative Approach to Understanding Quality of Life in Pediatric Palliative Care. *Palliative Care & Medicine* 2012.

24. Wolfe J, Orellana L, Ullrich C, et al. Symptoms and Distress in Children With Advanced Cancer: Prospective Patient-Reported Outcomes From the PediQUEST Study. *Journal of Clinical Oncology* 2015; **33**(17): 1928-U101.
25. Dupuis LL, Ethier MC, Tomlinson D, Hesser T, Sung L. A systematic review of symptom assessment scales in children with cancer. *Bmc Cancer* 2012; **12**.
26. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.[Erratum appears in Int J Surg. 2010;8(8):658]. *International Journal Of Surgery* 2010; **8**(5): 336-41.
27. Janssens A, Williams J, Tomlinson R, Logan S, Morris C. Health outcomes for children with neurodisability: what do professionals regard as primary targets? *Archives of Disease in Childhood* 2014; **99**(10): 927-32.
28. Hawker S, Payne S, Kerr C, Hardey M, Powell J. Appraising the evidence: reviewing disparate data systematically. *Qual Health Res* 2002; **12**(9): 1284-99.
29. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg* 2014; **12**(12): 1500-24.
30. Terwee CB, Bot SD, de Boer MR, et al. Quality Criteria were proposed for measurement properties of health status questionnaires *Journal of Clinical Epidemiology* 2007; **60**: 34-42
31. Whittemore R, Knafl K. The integrative review: updated methodology. *J Adv Nurs* 2005; **52**(5): 546-53.
32. Sandelowski M, Voils CI, Barroso J. Defining and Designing Mixed Research Synthesis Studies. *Research in the schools : a nationally refereed journal sponsored by the Mid-South Educational Research Association and the University of Alabama* 2006; **13**(1): 29.
33. Matza LS, Patrick DL, Riley AW, et al. Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. *Value Health* 2013; **16**(4): 461-79.
34. Arbuckle R, Abetz-Webb L. "Not Just Little Adults": Qualitative Methods to Support the Development of Pediatric Patient-Reported Outcomes. *Patient-Patient Centered Outcomes Research* 2013; **6**(3): 143-59.
35. World Health Organisation. WHO Definition of Palliative Care. 2002. http://www.who.int/cancer/palliative/definition/en/.
36. WorldHealth Organisation. International classification of Functioning, Disability, and Health: Children and Youth Version. 2007.
37. www.nihpromis.org/documents.
38. Anthony SJ, Dix D, Klaassen R, Scheinemann K, Sung L, Klassen A. Important factors to understanding quality of life according to children with cancer and childhood cancer survivors. *Pediatric Blood and Cancer* 2012; **59 (6)**: 1120.
39. Donnelly JP, Huff SM, Lindsey ML, McMahon KA, Schumacher J. The needs of children with life-limiting conditions: A healthcare-provider-based model. *American Journal of Hospice & Palliative Medicine* 2005; **22**(4): 259-67.
40. Wolfe J, Orellana L, Cook EF, et al. Improving the care of children with advanced cancer by using an electronic patient-reported feedback intervention: results from the PediQUEST randomized controlled trial. *Journal of Clinical Oncology* 2014; **32**(11): 1119-26.
41. Soanes L, Hargrave D, Smith L, Gibson F. What are the experiences of the child with a brain tumour and their parents? *Eur J Oncol Nurs* 2009; **13**(4): 255-61.
42. Beaune L, Forrest CR, Keith T. Adolescents' perspectives on living and growing up with Treacher Collins syndrome: A qualitative study. *Cleft Palate-Craniofacial Journal* 2004; **41**(4): 343-50.
43. Collins JJ. Palliative care and the child with cancer. *Hematology-Oncology Clinics of North America* 2002; **16**(3): 657-+.
44. Petersen C, Schmidt S, Power M, Bullinger M, Grp D. Development and pilot-testing of a health-related quality of life chronic generic module for children and adolescents with chronic health conditions: A European perspective. *Quality of Life Research* 2005; **14**(4): 1065-77.

45. Woodgate RL. Feeling states - A new approach to understanding how children and adolescents with cancer experience symptoms. *Cancer Nursing* 2008; **31**(3): 229-38.
46. Darcy L, Knutsson S, Huus K, Enskar K. The everyday life of the young child shortly after receiving a cancer diagnosis, from both children's and parent's perspectives. *Cancer Nursing* 2014; **37**(6): 445-56.
47. Woodgate RL, Degner LF. A substantive theory of Keeping the Spirit Alive: the Spirit Within children with cancer and their families. *J Pediatr Oncol Nurs* 2003; **20**(3): 103-19.
48. Woodgate RL, West CH, Tailor K. Existential Anxiety and Growth An Exploration of Computerized Drawings and Perspectives of Children and Adolescents With Cancer. *Cancer Nursing* 2014; **37**(2): 146-59.
49. Avoine-Blondin J, Lahaye M, Parent V, Duval M, Humbert N, Sultan S. Quality of life of children with cancer treated with palliative care: A qualitative study on professionals' perceptions. *Pediatric Blood and Cancer* 2014; **61**: S388.
50. Barrera M, Schulte F, Bartels U, et al. A randomized control trial to evaluate the efficacy of a group social skills intervention for childhood survivors of brain tumours. *Neuro-Oncology* 2012; **14**: i138.
51. Barnes MJ, Pressey J, Adams J, Hensler MA, Madan-Swain A. Physician and nurse beliefs of phase 1 trials in pediatric oncology. *Cancer Nursing* 2014; **37**(5): E48-E52.
52. Ronen GM, Rosenbaum P, Law M, Streiner DL. Health-related quality of life in childhood disorders: A modified focus group technique to involve children. *Quality of Life Research* 2001; **10**(1): 71-9.
53. Weaver MS, Heinze KE, Bell CJ, et al. Establishing psychosocial palliative care standards for children and adolescents with cancer and their families: An integrative review. *Palliative medicine* 2016; **30**(3): 212-23.
54. Woodgate RL, West CH, Tailor K. Existential anxiety and growth: an exploration of computerized drawings and perspectives of children and adolescents with cancer. *Cancer Nurs* 2014; **37**(2): 146-59.
55. Woodgate RL. Feeling states: a new approach to understanding how children and adolescents with cancer experience symptoms. *Cancer Nurs* 2008; **31**(3): 229-38.
56. Zelcer S, Cataudella D, Cairney AE, Bannister SL. Palliative care of children with brain tumors: a parental perspective. *Arch Pediatr Adolesc Med* 2010; **164**(3): 225-30.
57. Hongo T, Watanabe C, Okada S, et al. Analysis of the circumstances at the end of life in children with cancer: Symptoms, suffering and acceptance. *Pediatrics International* 2003; **45**(1): 60-4.
58. Khadra C, Le May S, Tremblay I, et al. Development of the adolescent cancer suffering scale. *Pain Research and Management* 2015; **20**(4): 213-9.
59. Jacobs S, Perez J, Cheng YI, Sill A, Wang J, Lyon ME. Adolescent end of life preferences and congruence with their parents' preferences: results of a survey of adolescents with cancer. *Pediatr Blood Cancer* 2015; **62**(4): 710-4.
60. Oberholzer AE, Nel E, Myburgh CPH, Poggenpoel M. Exploring the needs and resources of children in a haematology-oncology unit. *Health SA Gesondheid (Online)* 2011; **16**(1): 1-12.
61. Ljungman G, Gordh T, Sorensen S, Kreuger A. Pain in paediatric oncology: interviews with children, adolescents and their parents. *Acta Paediatr* 1999; **88**(6): 623-30.
62. Drake R, Frost J, Collins JJ. The symptoms of dying children. *Journal of Pain & Symptom Management* 2003; **26**(1): 594-603.
63. Poder U, Ljungman G, von Essen L. Parents' perceptions of their children's cancer-related symptoms during treatment: a prospective, longitudinal study. *Journal of Pain & Symptom Management* 2010; **40**(5): 661-70.
64. Jalmsell L, Kreicbergs U, Onelov E, Steineck G, Henter J-I. Symptoms affecting children with malignancies during the last month of life: a nationwide follow-up. *Pediatrics* 2006; **117**(4): 1314-20.
65. Hendricks-Ferguson V. Physical symptoms of children receiving pediatric hospice care at home during the last week of life. *Oncology Nursing Forum* 2008; **35**(6): E108-15.
66. Hongo T, Watanabe C, Okada S, et al. Analysis of the circumstances at the end of life in children with cancer: symptoms, suffering and acceptance. *Pediatrics International* 2003; **45**(1): 60-4.
67. Theunissen JMJ, Hoogerbrugge PM, van Achterberg T, Prins JB, Vernooij-Dassen MJFJ, van den Ende CHM. Symptoms in the palliative phase of children with cancer. *Pediatric Blood & Cancer* 2007; **49**(2): 160-5.

68. Cheatham SLH. Neurodevelopmental outcomes in infants with hypoplastic left heart syndrome after Hybrid Stage I palliation. *Dissertation Abstracts International: Section B: The Sciences and Engineering* 2013; **74**(5-B(E)): No Pagination Specified.
69. Edwards KE, Neville BA, Cook EF, Jr., Aldridge SH, Dussel V, Wolfe J. Understanding of prognosis and goals of care among couples whose child died of cancer. *Journal of Clinical Oncology* 2008; **26**(8): 1310-5.
70. Goldman A. ABC of palliative care. Special problems of children. *BMJ* 1998; **316**(7124): 49-52.
71. Olagunju AT, Sarimiye FO, Olagunju TO, Habeebu MY, Aina OF. Child's symptom burden and depressive symptoms among caregivers of children with cancers: an argument for early integration of pediatric palliative care. *Ann Palliat Med* 2016.
72. Wise BV. In their own words: The lived experience of pediatric liver transplantation. *Qualitative Health Research* 2002; **12**(1): 74-90.
73. Enskar K, Carlsson M, Golsater M, Hamrin E, Kreuger A. Life situation and problems as reported by children with cancer and their parents. *Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses* 1997; **14**(1): 18-26.
74. Montoya-Juarez R, Garcia-Caro M, Schmidt-Rio-Valle J, et al. Suffering indicators in terminally ill children from the parental perspective. *European Journal of Oncology Nursing* 2013; **17**(6): 720-5.
75. Bjork M, Nordstrom B, Hallstrom I. Needs of young children with cancer during their initial hospitalization: an observational study. *Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses* 2006; **23**(4): 210-9.
76. Goldman A, Hewitt M, Collins GS, Childs M, Hain R. Symptoms in children/young people with progressive malignant disease: United Kingdom Children's Cancer Study Group/Paediatric Oncology Nurses Forum Survey. *Pediatrics* 2006; **117**(6): e1179-e86.
77. Macartney G, VanDenKerkhof E, Harrison MB, Stacey D. Symptom Experience and Quality of Life in Pediatric Brain Tumor Survivors: A Cross-Sectional Study. *Journal of Pain and Symptom Management* 2014; **48**(5): 957-67.
78. Garvie PA, He J, Wang J, D'Angelo LJ, Lyon ME. An exploratory survey of end-of-life attitudes, beliefs, and experiences of adolescents with HIV/AIDS and their families. *Journal of Pain & Symptom Management* 2012; **44**(3): 373-85.e29.
79. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *British Journal of Dermatology* 2006; **155**(1): 145-51.
80. Allard A, Fellowes A, Shilling V, Janssens A, Beresford B, Morris C. Key health outcomes for children and young people with neurodisability: qualitative research with young people and parents. *Bmj Open* 2014; **4**(4).
81. Veldhuijzen van Zanten SEM, van Meerwijk CLLI, Jansen MHA, et al. Palliative and end-of-life care for children with diffuse intrinsic pontine glioma: results from a London cohort study and international survey. *Neuro-Oncology* 2016; **18**(4): 582-8.
82. Dupuis LL, Milne-Wren C, Cassidy M, et al. Symptom assessment in children receiving cancer therapy: the parents' perspective. *Supportive Care in Cancer* 2010; **18**(3): 281-99.
83. Weaver MS, Baker JN, Gattuso JS, Gibson DV, Sykes AD, Hinds PS. Adolescents' preferences for treatment decisional involvement during their cancer. *Cancer* 2015; **121**(24): 4416-24.
84. Yeh CH, Wang CH, Chiang YC, Lin L, Chien LC. Assessment of Symptoms Reported by 10- to 18-Year-Old Cancer Patients in Taiwan. *Journal of pain and symptom management* 2009; **38**(5): 738-46.
85. Hinds PS, Drew D, Oakes LL, et al. End-of-life care preferences of pediatric patients with cancer. *Journal of Clinical Oncology* 2005; **23**(36): 9146-54.
86. Downing J, Jassal SS, Matthews L, Britts H, Friedrichsdorf SJ. Pediatric Pain Management in Palliative Care. *Pain Manag* 2015; **5**.
87. Nakawesi J, Kasirye I, Kavuma D, et al. Palliative care needs of HIV exposed and infected children admitted to the inpatient paediatric unit in Uganda. *ecancermedicalscience* 2014; **8 (no pagination)**(A489).

88. Enskar. K, Carlson M, Harmin E, Kreuger A. Swedish Health Care Personnel's Perceptions of Disease and Treatment- Related Problems Experienced by Children With Cancer and Their Families. *Journal of Pediatric Oncology Nursing* 1996; **13**(2): 61-70.
89. Hedstrom M, Haglund K, Skolin I, von Essen L. Distressing events for children and adolescents with cancer: child, parent, and nurse perceptions. *J Pediatr Oncol Nurs* 2003; **20**(3): 120-32.
90. Balkin EM, Wolfe J, Ziniel SI, et al. Physician and parent perceptions of prognosis and end-of-life experience in children with advanced heart disease. *Journal of palliative medicine* 2015; **18**(4): 318-23.
91. Ananth P, Melvin P, Feudtner C, Wolfe J, Berry JG. Hospital Use in the Last Year of Life for Children With Life-Threatening Complex Chronic Conditions. *Pediatrics* 2015; **136**(5): 938-46.
92. Hesseling PB, Molyneux E, Tchintseme F, et al. Treating Burkitt's lymphoma in Malawi, Cameroon, and Ghana. *Lancet Oncology* 2008; **9**(6): 512-3.
93. Momani TG, Mandrell BN, Gattuso JS, West NK, Taylor SL, Hinds PS. Children's perspective on health-related quality of life during active treatment for acute lymphoblastic leukemia: an advanced content analysis approach. *Cancer Nurs* 2015; **38**(1): 49-58.
94. Ito Y, Okuyama T, Kamei M, et al. Good death for children with cancer: a qualitative study. *Japanese Journal of Clinical Oncology* 2015; **45**(4): 349-55.
95. Barrera M, D'Agostino N, Gammon J, Spencer L, Baruchel S. Health-related quality of life and enrollment in phase 1 trials in children with incurable cancer. *Palliative & Supportive Care* 2005; **3**(3): 191-6.
96. Ronen GM, Rosenbaum P, Law M, Streiner DL. Health-related quality of life in childhood epilepsy: the results of children's participation in identifying the components. *Developmental Medicine and Child Neurology* 1999; **41**(8): 554-9.
97. Lavy V. Presenting symptoms and signs in children referred for palliative care in Malawi. *Palliative medicine* 2007; **21**(4): 333-9.
98. McHugh G, Rylance J, Mujuru H, et al. Chronic Morbidity Among Older Children and Adolescents at Diagnosis of HIV Infection. *Journal of acquired immune deficiency syndromes (1999)* 2016; **73**(3): 275-81.
99. Nicholas DB, Picone G, Selkirk EK. The lived experiences of children and adolescents with end-stage renal disease. *Qualitative Health Research* 2011; **21**(2): 162-73.
100. Allen DA, Affleck G, Tennen H, McGrade BJ, Ratzan S. Concerns of children with a chronic illness: a cognitive-developmental study of juvenile diabetes. *Child: Care, Health & Development* 1984; **10**(4): 211-8.
101. Woodgate RL, Degner LF, Yanofsky R. A different perspective to approaching cancer symptoms in children. *Journal of Pain & Symptom Management* 2003; **26**(3): 800-17.
102. Ravens-Sieberer U, Bullinger M. Assessing health-related quality of life in chronically ill children with the German KINDL: first psychometric and content analytical results. *Qual Life Res* 1998; **7**(5): 399-407.
103. Punpanich W, Gorbach PM, Detels R. Impact of paediatric human immunodeficiency virus infection on children's and caregivers' daily functioning and well-being: a qualitative study. *Child Care Health and Development* 2012; **38**(5): 714-22.
104. Freeman K, O'Dell C, Meola C. Childhood brain tumors: children's and siblings' concerns regarding the diagnosis and phase of illness. *Journal of Pediatric Oncology Nursing* 2003; **20**(3): 133-40.
105. Momani TG, Mandrell BN, Gattuso JS, West NK, Taylor SL, Hinds PS. Children's Perspective on Health-Related Quality of Life During Active Treatment for Acute Lymphoblastic Leukemia An Advanced Content Analysis Approach. *Cancer Nursing* 2015; **38**(1): 50-9.
106. Lau BD, Aslakson RA, Wilson RF, et al. Methods for improving the quality of palliative care delivery: A systematic review. *American Journal of Hospice & Palliative Medicine* 2014; **31**(2): 202-10.
107. Avoine-Blondin J, Parent V, Lahaye M, Humbert N, Duval M, Sultan S. Identifying domains of quality of life in children with cancer undergoing palliative care: A qualitative study with professionals. *Palliat Support Care* 2017: 1-10.
108. Kamper R, Van Cleve L, Savedra M. Children with advanced cancer: responses to a spiritual quality of life interview. *Journal for Specialists in Pediatric Nursing: JSPN* 2010; **15**(4): 301-6.
109. Forrester AB, Barton-Gooden A, Pitter C, Lindo JLM. The lived experiences of adolescents with sickle cell disease in Kingston, Jamaica. *International Journal of Qualitative Studies on Health and Well-Being* 2015; **10**.

110. Li HCW, Chung OKJ, Chiu SY. The Impact of Cancer on Children's Physical, Emotional, and Psychosocial Well-being. *Cancer Nursing* 2010; **33**(1): 47-54.
111. Garvie PA, He J, Wang J, D'Angelo LJ, Lyon ME. An exploratory survey of end-of-life attitudes, beliefs, and experiences of adolescents with HIV/AIDS and their families. *J Pain Symptom Manage* 2012; **44**(3): 373-85.
112. Woodgate RL, Degner LF. A substantive theory of Keeping the Spirit Alive: the Spirit Within children with cancer and their families. *Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses* 2003; **20**(3): 103-19.
113. Taylor LK, Miller M, Joffe T, et al. Palliative care in Yorkshire, UK 1987-2008: survival and mortality in a hospice. *Archives of Disease in Childhood* 2010; **95**(2): 89-93.
114. McClearly J, Kanesathasan A, Barakash J, et al. Foundation for Future : Meeting the Pyschosocial Needs of Children Living With HIV in South Africa and Uganda *JournaL of HIV/AIDS and Social Services* 2013 **12**: 49-62.
115. Punpanich W, Detels R, Gorbach PM, Leowsrisook P. Understanding the psychosocial needs of HIV-infected children and families: a qualitative study. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet* 2008; **91 Suppl 3**: S76-84.
116. Fraser DFG. Strangers in their own land : Friendhsip issues when children have cancer *Journal of Research in special Educational Needs* 2003 **3**(3): 147-53
117. Taylor RM, Franck LS, Dhawan A, Gibson F. The Stories of Young People Living With a Liver Transplant. *Qualitative Health Research* 2010; **20**(8): 1076-90.
118. Einberg EL, Svedberg P, Enskar K, Nygren JM. Friendship Relations From the Perspective of Children With Experience of Cancer Treatment: A Focus Group Study With a Salutogenic Approach. *Journal of Pediatric Oncology Nursing* 2015; **32**(3): 153-64.
119. Hedstrom M, Haglund K, Skolin I, von Essen L. Distressing events for children and adolescents with cancer: child, parent, and nurse perceptions. *Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses* 2003; **20**(3): 120-32.
120. Ljungman G, Gordh T, Sorensen S, Kreuger A. Pain in paediatric oncology: interviews with children, adolescents and their parents. *Acta Paediatrica* 1999; **88**(6): 623-30.
121. Cataudella DA, Zelcer S. Psychological experiences of children with brain tumors at end of life: parental perspectives. *Journal of palliative medicine* 2012; **15**(11): 1191-7.
122. Hinds PS, Gattuso JS, Fletcher A, et al. Quality of life as conveyed by pediatric patients with cancer. *Quality of Life Research* 2004; **13**(4): 761-72.
123. Griffiths M, Schweitzer R, Yates P. Childhood Experiences of Cancer: An Interpretative Phenomenological Analysis Approach. *Journal of Pediatric Oncology Nursing* 2011; **28**(2): 83-92.
124. Woodgate RL, Degner LF. Expectations and beliefs about children's cancer symptoms: perspectives of children with cancer and their families. *Oncology Nursing Forum* 2003; **30**(3): 479-91.
125. Jacobs S, Perez J, Cheng YI, Sill A, Wang JC, Lyon ME. Adolescent End of Life Preferences and Congruence With Their Parents' Preferences: Results of a Survey of Adolescents With Cancer. *Pediatric Blood & Cancer* 2015; **62**(4): 710-4.
126. Ruhe KM, Badarau DO, Brazzola P, Hengartner H, Elger BS, Wangmo T. Participation in pediatric oncology: views of child and adolescent patients. *Psychooncology* 2015; **17**(10).
127. Enskar K. Being an Expert Nurse in Pediatric Oncology Care: Nurses' Descriptions in Narratives. *Journal of Pediatric Oncology Nursing* 2012; **29**(3): 151-60.
128. Kuan GL, Low WY. Parents' perspectives on the important aspects of care in children dying from life limiting conditions: A qualitative study. *Medical Journal of Malaysia* 2015; **70**(5): 295-9.
129. de Aquino AM, De Conti L, Pedrosa A. Construction of meanings about illness and death in the narratives of children with cancer. *Psicologia: Reflexao e Critica* 2014; **27**(3): 599-606.
130. Stegenga K, Ward-Smith P. On receiving the diagnosis of cancer: the adolescent perspective. *J Pediatr Oncol Nurs* 2009; **26**(2): 75-80.
131. Solomon GE, Cassimatis NL. On facts and conceptual systems: young children's integration of their understandings of germs and contagion. *Dev Psychol* 1999; **35**(1): 113-26.

132. Stevenson M, Achille M, Lugasi T. Pediatric palliative care in Canada and the United States: a qualitative metasummary of the needs of patients and families. *Journal of Palliative Medicine* 2013; **16**(5): 566-77.
133. Temel JS, Greer JA, El-Jawahri A, et al. Effects of Early Integrated Palliative Care in Patients With Lung and GI Cancer: A Randomized Clinical Trial. *J Clin Oncol* 2017; **35**(8): 834-41.
134. Mularski RA, Dy SM, Shugarman LR, et al. A systematic review of measures of end-of-life care and its outcomes. *Health Serv Res* 2007; **42**(5): 1848-70.
135. The National Academies Press. Institute of Medicine. Crossing the quality chasm: a new health system for the 21st century. Washington, DC:; 2001 page 6
136. Picker Institute. Principles of patient centred care. 2015.
137. Wallander JL, Schmitt M, Koot HM. Quality of life measurement in children and adolescents: Issues, instruments, and applications. *Journal of Clinical Psychology* 2001; **57**(4): 571-85.
138. Davis E, Nicolas C, Waters E, et al. Parent-proxy and child self-reported health-related quality of life: using qualitative methods to explain the discordance. *Quality of Life Research* 2007; **16**(5): 863-71.
139. Christ G, H. Healing Children's Grief New York . Oxford Oxford Uinversity Press Inc.; 2000.
140. Wilkins ML, Dallas RH, Fanone KE, Lyon ME. Pediatric palliative care for youth with HIV/AIDS: systematic review of the literature. *HIV/AIDS (Auckland, NZ)* 2013; **5**: 165-79.
141. Higginson IJ. End-of-life care: lessons from other nations. *J Palliat Med* 2005; **8 Suppl 1**: S161-73.
142. Knapp C, Madden V. Conducting outcomes research in pediatric palliative care. *American Journal of Hospice & Palliative Medicine* 2010; **27**(4): 277-81.
143. Hain R, Devins M, Hastings R, Noyes J. Paediatric palliative care: development and pilot study of a 'Directory' of life-limiting conditions. *BMC Palliative Care* 2013; **12**(1): 43.
144. Harding R, Simon ST, Benalia H, et al. The PRISMA Symposium 1: outcome tool use. Disharmony in European outcomes research for palliative and advanced disease care: too many tools in practice. *J Pain Symptom Manage* 2011; **42**(4): 493-500.
145. Simon ST, Higginson IJ, Harding R, et al. Enhancing patient-reported outcome measurement in research and practice of palliative and end-of-life care. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2012; **20**(7): 1573-8.
146. Hudson BF, Oostendorp LJ, Candy B, et al. The under reporting of recruitment strategies in research with children with life-threatening illnesses: A systematic review. *Palliative medicine* 2016.
147. Wallander JL, Schmitt M, Koot HM. Quality of life measurement in children and adolescents: issues, instruments, and applications. *J Clin Psychol* 2001; **57**(4): 571-85.